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09/515,276	02/29/2000	Marc R. Montminy	SALK1650-2	1983

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 32/16

Application Number: 09/515,276
Filing Date: February 29, 2000
Appellant(s): MONTMINY, MARC R.

Barry S. Wilson

For Appellant

EXAMINER'S ANSWER

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

The rejection of claims 1-7, 12, and 17 stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Merck Research Laboratories. The Merck Manual of Diagnosis and Therapy, Seventeenth Edition, 1999, pp. 169-177.

Mayr, B. et al. "Transcriptional Regulation by the Phosphorylation-Dependent Factor CREB" Nature Reviews, Vol 2, (August 2001), pp. 599-609.

Herzig, S. et al. "CREB regulates hepatic gluconeogenesis through the coactivator PGC-1" Nature, Vol. 413, September 2001, pp. 179-183.

5,750,336	Montminy	5-1998
6,063,583	Montminy	5-2000

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-7, 12, and 17 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining enablement include the breadth of the claims, the nature of the invention, the state of the prior art; the level of one of ordinary skill, the level of predictability in the art, the amount of direction provided by the

inventor, the existence of working examples; and the quantity of experimentation needed to make or use the invention.

The claims are drawn to a method of treating diabetes by administering a compound that inhibits binding of cyclic AMP response element binding protein, CREB, to CREB binding protein, CBP, or disrupts a complex comprising CREB and CBP; the inhibiting or disrupting compound is identified by Appellant's patented method (US 6,063,583). The state of the prior art is what one skilled in the art would have known, at the time the application was filed, about the subject matter to which the claimed invention pertains. The application being appealed is a divisional of application 08/961739, filed October 31, 1997, now US Patent No. 6,063,583, which is a continuation-in-part of 08/194468, now US Patent 5,750,336, filed February 10, 1994. The appealed claims have an effective filing date of October 31, 1997, since neither the particular identification method for compounds nor a diabetes treatment method is disclosed in 08/194468. The state of the prior art at the time the invention was made is appropriately determined as of no earlier than October 1997. The Merck Manual of Diagnosis and Therapy, Seventeenth Edition, published 1999, provides at least an indication of the state of the art with respect to diabetes treatment at or about the time the invention was made (The Sixteenth Edition of the Merck Manual of Diagnosis and Therapy was published in 1992.). The Merck Manual does not indicate that inhibition or disruption of CREB-CPB binding is a known mechanism of action for any recognized diabetes treatment, including insulin, the sulfonylureas, and various hyperglycemic drugs. Since the state of the art at the time the invention was made provides no

information that would aid one of skill in the art in knowing how to treat diabetes using a compound that inhibits or disrupts CREB-CPB binding, in the absence of evidence to the contrary, one wishing to practice the claimed invention must rely solely on Appellant's disclosure for guidance.

The specification of the instant application mentions diabetes treatment in five places:

(1) In the last sentence of the Abstract: "In still another aspect, methods employing compounds which inhibit intracellular signal-induced response pathways have been developed for the treatment of diabetes mellitus."

(2) At page 1, lines 24-26: "In yet another aspect, the present invention relates to methods for treating diabetes mellitus."

(3) At page 3, line 28-page 4, line 8: "The ability to repress intracellular signal-induced response pathways is an important mechanism in negative control of gene expression. Selective disruption of such pathways would allow the development of therapeutic agents capable of treating a variety of disease states related to improper activation and/or expression of specific transcription factors. For example, in patients with non-insulin dependent diabetes mellitus (NIDDM), hyperglycemia develops, in part as a result of ß cell failure secondary to chronic insulin resistance. This hyperglycemia appears to be exacerbated by hyperglucagonemia and increased hepatic gluconeogenesis. cAMP appears to be the major starvation state signal which triggers glucagon gene expression as well as transcription of PEPCK, the rate limiting enzyme in gluconeogenesis."

(4). At page 4, line 29-page 5, line 2: "In still another aspect, an assay is provided to identify compounds which have the binding and/or activation properties characteristic of CREB binding protein. In still another aspect, methods employing compounds which inhibit intracellular signal-induced response pathways have been developed for the treatment of diabetes mellitus."

(5) At page 20, lines 1-11: "In accordance with a still further embodiment of the present invention, there are provided methods for treating diabetes mellitus, said method comprising contacting a biological system with an amount of an effective amount of a compound which inhibits binding of CREB to CBP. Such methods ameliorate hyperglycemia associated with diabetes mellitus by modulating gluconeogenesis and/or hyperglucagonemia. Particularly, such methods employ compounds which disrupt the formation of CREB:CBP complexes, thus inhibiting transcription of PEPCK or glucagon gene."

The specification provides Examples I-V, all of which are *in vitro* studies that concern the properties of CBP and the nature of its interactions with other proteins. The specification provides no basis for correlating results obtained in these *in vitro* studies with any beneficial effect to be had by practicing a method of treating diabetes by administering a compound that inhibits binding of cyclic AMP response element binding protein, CREB, to CREB binding protein, CBP, or that disrupts a complex comprising CREB and CBP. Appellant's disclosure provides, at best, predicted results rather than results actually obtained and does not alone provide sufficient guidance for one of skill in the art to practice the invention as claimed without undue experimentation.

(11) Response to Argument

Appellant has argued that the Examiner has "required Appellant to demonstrate that the inventive mechanism of action was accepted in the art prior to the filing of the application"; has asserted that the fact that Appellant's [invention's] mechanism of action was not disclosed in the Merck Manual lacks relevance to the question of enablement; and has cited post filing publications (Mayr et al. and Herzig et al., now made of record) by the inventor "describing the inventive methods and asserting its use in treating diabetes mellitus." Appellant has stated that the Examiner "appears to accept that the screening method for identifying inhibiting compounds described in the application is enabled," and that the Examiner "continues to insist" that clinical data are required to demonstrate that a compound exists that has both the binding-inhibitory effect required and is effective to treat a human with diabetes. Appellant has argued that there is no evidence that the Merck Manual is a reliable source for the latest in diabetes treatment methods and mechanisms of action and that it does not provide mention of new methods of treatment as represented in newly issued patents, of which Appellant cites ten by patent number. Appellant has argued that the Mayr et al. reference states that CREB functions in glucose homeostasis and that the conclusions stated in Mayr et al. are consistent with Appellant's disclosure teaching involvement of CREB-CBP complex in diabetes. Appellant has argued that the Herzig et al. article reports that CREB controls glucose homeostasis through expression of gluconeogenic enzymes via the transactivator PGC-1, and uses normal and diabetic animals to show that reduced CREB activity causes fasting hyperglycemia *in vivo*, which Herzig et al. states "is

correlated with Type II diabetes." Appellant points to the specification as providing guidance in formulation and dosage. Appellant has argued that there is no *per se* requirement for human clinical data to enable a method of therapy. Appellant has alleged that the Examiner failed to consider the Mayr et al. and the Herzig et al. references as evidence because they were published after the filing date of the application and use methods to obtain results that go beyond those instantly disclosed and has urged that they are relied upon to prove the truth of statements in Appellant's disclosure rather than to supplement the disclosure itself.

Appellant's arguments have been considered but not found to be persuasive. The Examiner has not required Appellant to demonstrate that the inventive mechanism of action was accepted in the prior art, and has not required Appellant to provide clinical data; rather, the citation of material from the Merck Manual was done purely to help establish the state of the art at, or about, the time the invention was made. Further, the Examiner has made no mention of the presence or absence of clinical data, but rather has noted that Appellant has provided no basis for correlation of the *in vitro* examples provided in the specification with an *in vivo* treatment for diabetes using a compound that is specified only by a method for identifying it. It is agreed that a method to identify compounds which disrupt complex comprising CREB and CBP is enabled; see claims 1-6 of US Patent No. 6,063,583. With respect to the ten patents cited by Appellant to support the assertion that patents have been issued whose mechanism of action is not disclosed in the Merck Manual, the assertion is not evaluated here since Appellant has provided no detailed discussion of the mechanisms of action of treatment represented in

each of the patents and no discussion of how such information is relevant to the appealed claims. It is noted that the prosecution of a particular patent application generally has no bearing on the prosecution of any other application. With respect to the citation of the Mayr et al. and the Herzig et al. references, a later dated publication cannot supplement an insufficient disclosure in a prior dated application to make it enabling and cannot be used to show what was known at the time of filing. With respect to Appellant's assertion that the Mayr et al. and Herzig et al. are relied upon to prove the truth of statements in Appellant's disclosure rather than to supplement the disclosure itself, even if Appellant relies upon Mayr et al. to show that CREB functions in glucose homeostasis and that the conclusions stated in Mayr et al. are consistent with Appellant's disclosure teaching involvement of CREB-CBP complex in diabetes, the Mayr et al. reference does not teach that a compound identified by Appellant's method has a beneficial effect when used to treat diabetes. Even if Appellant relies upon Herzig et al. to show that CREB controls glucose homeostasis through expression of gluconeogenic enzymes via the transactivator PGC-1, and uses normal and diabetic animals to show that reduced CREB activity causes fasting hyperglycemia *in vivo*, Herzig et al. does not teach that a compound identified by Appellant's method has a beneficial effect when used to treat diabetes. Further, Herzig et al., published in September 2001, supports the unpredictability remaining in the field nearly four years after Appellant's effective filing date: "The effect of A-CREB on liver gene expression suggests that CREB **may** constitute an ideal target for therapeutic intervention. Although use of a dominant negative inhibitor such as A-CREB may not be feasible in

this regard, small molecules that block CREB phosphorylation or disrupt recruitment of the CREB coactivator CBP (CREB binding protein) **may** prove effective. Such compounds **may** be particularly beneficial as adjunctive therapy in lowering fasting blood glucose levels in type II diabetes." (See Herzig et al., page 182, second column, second full paragraph; emphasis added.)

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Donna C. Wortman, Ph.D.
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Art Unit 1648

dcw
September 12, 2002

Conferees

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